

a particular challenge to HIV vaccine development. Our focus is to understand the dynamics of two of the most commonly tracked clinical markers of an HIV infection: CD4⁺ T cells/mm³ (CD4 count) and HIV RNA/ml (viral load).

Methods: We developed a stochastic system of differential equations to model HIV infection that uses equilibration, adaptation, and inheritance to model the initial infection as well as successive generations of viral lineages. The model allows viruses to generate new lineages in proportion to their viral load with an inherited fitness. These lineages compete for immune cells to infect and drive decline in CD4 count through a series of small adaptations. We use this model to demonstrate how viruses with a sufficiently high mutation rate could overcome the immune system, even when most changes are expected to be detrimental to viral fitness.

Results: We have calibrated our model to match viral load set points and rates of CD4 decline from 91 HIV-infected individuals studied longitudinally during early stages of the disease. Our model demonstrates how a genetically diverse population of viruses could be sustained in an environment with high rates of competition, turnover, and the development of an immune response. The underlying stochastic process also generates a phylogenetic structure which can be used to explore different hereditary patterns in the underlying viral lineages.

Conclusions: Our model demonstrates that the high rate of mutation and recombination in the HIV genome can contribute to slow disease progression. It suggests the diversity of HIV lineages is a consequence of lineages having similar fitness and the high levels of competition which create a balance in the expansion of existing lineages and their replacement by new lineages.

P39.02

Adaptation of HIV-1 Envelope Glycoprotein gp120 to Humoral Immunity over the Course of the Epidemic

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Background: Since 2009, a large panel of broad and potent monoclonal neutralizing antibodies (MoNabs) against HIV-1 have been isolated. These MoNabs can protect from HIV-1 infection and suppress established infection in animal models. Because their efficacy should be evaluated in human clinical trials, it is of importance to define the sensitivity of the most contemporary transmitted variants to these MoNabs. We, and others previously, reported that HIV-1 has become more resis-

tant to neutralization over the course of the epidemic (Bunnik *et al.*, Nature Med 2010, Bouvin-Pley *et al.*, PLoS Pathog 2013).

Methods: Here we extended the analyses to the most potent MoNabs described since then, either more recently isolated or improved by structure-based gene modifications.

Results: We fully confirmed the first observations showing an increasing resistance of HIV-1 clade B over time to MoNabs targeting the major gp120 epitopes but not to MoNabs targeting the gp41 MPER. Despite this evolution, some MoNabs still were able to neutralize efficiently the most recently transmitted HIV-1 variants (2006–2010). The most potent MoNabs were the bi-specific PG9- and PG16-iMab that alone were able to neutralize all variants at less than 0.4 mg/mL. The sensitivity to iMab remained similar over time, suggesting that the trend of increasing resistance to PG9-/PG16-iMab may be attributed only to the antigen binding domain of PG9/PG16. NIH45-46m2 (and -m7), 10-1074 and 10E8 were also highly potent and, if combined, reached the potency of PG9-/PG16-iMab. We also observed that 3BNC117 was almost as potent as the modified NIH45-46 antibodies, and that the lama-derived JM4IgG2b was the most potent Ab among those that do not target the major gp120 neutralizing epitopes.

Conclusions: These data clearly suggest a continuous drift of the *env* gene of HIV-1 clade B over the epidemic, and that not a single epitope is concerned but the entire gp120 as a whole. The consequences of this adaptation on the envelope functionality are being explored.

P39.03

Characterisation of Transmitted and Non-transmitted HIV in Index-recipient Transmission Pairs

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Background: Many of the viral and host factors associated with HIV transmission are still poorly understood. In 60–80% of the mucosal infections, a single transmitted/founder virus is responsible for the establishment of a productive infection, indicating a strong genetic bottleneck upon transmission. We aim to better understand the viral factors involved during transmission by studying the genetic variability and replicative characteristics of viruses isolated from transmission pairs.

Methods: We had access to blood samples from 5 index-recipient transmission pairs of MSM. All samples were obtained shortly after transmission. Plasma was used for full genome sequencing and PBMC were cocultured with HIV negative donor PBMC by limiting dilution to obtain biological clones.

Results: We isolated a total of 270 biological clones from the 5 transmission pairs. Nearly the complete gp120 from 7–18 clones was sequenced for each of the 10 individuals. As expected, these sequences group nicely with the plasma sequences. In only one